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Original Research

Coupling biomechanics to a cellular level model: An approach to patient-specific image driven multi-scale and multi-physics tumor simulation

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ABSTRACT

Modeling of tumor growth has been performed according to various approaches addressing different biocomplexity levels and spatiotemporal scales. Mathematical treatments range from partial differential equation based diffusion models to rule-based cellular level simulators, aiming at both improving our quantitative understanding of the underlying biological processes and, in the mid- and long term, constructing reliable multi-scale predictive platforms to support patient-individualized treatment planning and optimization. The aim of this paper is to establish a multi-scale and multi-physics approach to tumor modeling taking into account both the cellular and the macroscopic mechanical level. Therefore, an already developed biomodel of clinical tumor growth and response to treatment is self-consistently coupled with a biomechanical model. Results are presented for the free growth case of the imageable component of an initially point-like glioblastoma multiforme tumor. The composite model leads to significant tumor shape corrections that are achieved through the utilization of environmental pressure information and the application of biomechanical principles. Using the ratio of smallest to largest moment of inertia of the tumor material to quantify the effect of our coupled approach, we have found a tumor shape correction of 20% by coupling biomechanics to the cellular simulator as compared to a cellular simulation without preferred growth directions. We conclude that the integration of the two models provides additional morphological insight into realistic tumor growth behavior. Therefore, it might be used for the development of an advanced oncosimulator focusing on tumor types for which morphology plays an important role in surgical and/or radio-therapeutic treatment planning.

1. Introduction

Brain tumors remain a serious challenge in medicine and health sciences. More than half of them are of the glioblastoma multiforme type (Ohgaki and Kleihues, 2005), which is known for its extremely low treatment success rates. Among the European population, glioblastomas are the most frequent type of brain tumor, amounting to 69% of total incident cases with a prevalence of 3.55 cases per 100,000 persons per year adjusted to the European standard population (Ohgaki and Kleihues, 2005). Survival rates are observed to be 42.4% at 6 months, 17.7% at one year, and 3.3% at 2 years (Ohgaki and Kleihues, 2005). Modeling of these tumors is expected to significantly support the optimization of treatment planning and delivery. At the same time it can provide an improved understanding of the underlying multi-scale mechanisms of tumor development and dynamics.

Therefore, the growth and dynamics of brain tumors and especially of glioblastoma multiforme has been extensively studied through different computational approaches. Generic tumor modeling methods along with more specialized glioma simulation techniques have been devised for this purpose (Swanson et al., 2002; Stamatakos et al., 2002, 2006, 2010; Murray, 2003; Dionysiou et al., 2004; Clatz et al., 2005; Frieboes et al., 2006; Guiot et al., 2006; Hogea et al., 2007, 2008; Ramis-Conde et al., 2008; Graf et al., 2009; Deisboeck et al., 2009; Stamatakos, 2011). The major approaches include reaction-diffusion, diffusion coupled with biomechanics and discrete entity – discrete event cellular level based simulation focusing on cell cycling, necrosis, apoptosis, etc. The last mentioned model (Stamatakos et al., 2002, 2006, 2010; Dionysiou et al., 2004; Stamatakos, 2011), while providing a detailed description of the cellular evolution of the imageable component of the tumor, assumes a conformal expansion or shrinkage of an already large imageable tumor. Although this may be a plausible gross first approximation regarding tumor morphology, it may also be accompanied by an error in the detailed tumor shape prediction. This remark has motivated the coupling of

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the biological with a biomechanical model which is the subject of the present paper.

This work is part of the European Commission funded ContraCancrum project. The latter stands for Clinically Oriented Translational Cancer Multilevel Modeling and aims at developing a composite multilevel platform for simulating malignant tumor development and tissue response to treatment schedules. The ContraCancrum integrated tumor simulator encompasses a set of biological and physical models along with a wide range of methodological mathematical approaches spanning from cellular automata and Monte Carlo techniques to Finite Element approaches for partial differential equations. In this paper we present a novel approach addressing different spatiotemporal scales of biocomplexity by combining biomechanical stress/strain calculations with a cellular level based tumor simulation. It is important to note that both the biomechanical simulation and the cellular level based tumor simulation are self-contained models which can be run independently. However, both models in their entire complexity can be coupled in a self-consistent manner, yielding results taking into account both models.

The paper is organized as follows: Section 2 describes the two components of the integrated approach, namely the mechanical stress–strain computation in Section 2.1 and the cellular level simulator in the subsequent Section 2.2, followed by an explanation of the coupling approach. Section 3 presents illustrative results of an application of the composite model to glioblastoma multiforme, where a pronounced effect of the coupling of the two independent models can be observed. The paper concludes with a discussion of the in silico findings (Section 4) followed by the conclusions and an overall outlook (Section 5).

2. Material and methods

2.1. Stress/strain calculation

A fully automatic algorithm has been implemented using the Visualization Toolkit (VTK 5.6) which generates a voxel-based Finite Element mesh from segmented MRI image data. The patient-specific model includes the skull, white and gray matter as well as ventricles. In order to avoid sharp edges which might accumulate spurious stress concentration, element smoothing of the external surface and of interfaces between different materials is subsequently applied, which reduces peak stresses and improves accuracy. Finally, distorted elements are corrected by prism division, resulting in a refined mesh suitable for the finite element method (Bardyn et al., 2010).

For the solution of the mechanical deformation problem in a finite element formulation, the open-source software package FEBio (Version 1.2.2) (Maas et al., 2010) has been chosen as it is actively supported and can be used with the Pardiso solver (Schenk et al., 2008), which opens up the possibility to run in parallel, allowing for large three-dimensional meshes. We solve a linear elastic model using spatially dependent mechanical parameters as obtained from the segmentation. In order to simulate volume change in a generic manner, an arbitrary uniform strain in all three principal directions can be prescribed to each volume element, enabling it to model tumor growth and shrinkage. Thereby, a specific volume growth factor can be applied to any given volume element.

Formally, the linear elastic problem for isotropic materials is defined as the solution of

$$-\nabla\lambda(\nabla\cdot\mathbf{u}) - (\nabla\cdot\mu\nabla)\mathbf{u} - \nabla\cdot\mu(\nabla\mathbf{u})^T = \mathbf{f}, \tag{1}$$

where λ and μ are the so-called Lamé parameters, which can be easily related to the physically more intuitive Young's modulus E and Poisson ratio ν by

$$\mu = \frac{E}{2(1+\nu)} \tag{2}$$

$$\lambda = \frac{2\mu\nu}{1-2\nu}. \tag{3}$$

In this formulation, $\mathbf{u}$ describes the displacement of nodes we are interested in solving for, whereas $\mathbf{f}$ represents an externally applied force.

Physically, Eq. (1) describes how solid bodies deform and how internal stress is distributed under prescribed loading conditions. The underlying assumption is a linear relationship between the components of stress and strain. This formulation is well suited for Finite Element analysis and has been successfully applied to a wide range of problems and materials. Apart from the assumption of linearity, we also assume isotropic materials, which reduces the number of material parameters to two as shown in Eq. (1). The reasons for the assumption of isotropy with respect to mechanical properties are both a reduction of computational complexity and the difficulty to obtain established values for anisotropic parameters. However, this isotropy only implies that mechanical parameters at a given point do not depend on direction and therefore still allows a highly heterogeneous material composition.

The values for mechanical properties of different brain materials used in our simulations have been obtained from well established sources in the literature (Clatz et al., 2005) and are reproduced in Table 1. Since segmentation and meshing is performed on individual patients' images, this approach constitutes a patient-specific predictive model of internal mechanical behavior of tumor affected brain regions (Fig. 1).

This model is a continuum approach on a macroscopic level and by itself accurately describes how stress builds up and is distributed internally under given external loading conditions. Internal pressure, which is strongly supposed to affect the growth mechanism of tumors, can be calculated from stress in a straightforward manner. However, it does not incorporate any information about biological tumor growth mechanisms and cannot predict the amount each geometrical element will grow, which is the motivation for the inclusion of the subsequently described model.

2.2. Cellular level simulator

A brief outline of the cellular level based simulation model for solid tumor free growth and response to therapy is presented here, whereas a more detailed description can be found in (Stamatakos, 2011; Dionysiou et al., 2004; Stamatakos et al., 2002, 2006, 2010). The modeling approach is discrete in space and time and based on the concept of cellular automata. The model has been developed to support and incorporate individualized clinical data such as imaging data (e.g. CT, MRI, PET), including the definition of the tumor contour and internal metabolic tumor regions (proliferating, necrotic), histopathologic (e.g. type of tumor, grade) and the genetic data (e.g. p53 status, if available).

The algorithmic approach is outlined as follows: The anatomic region of interest is discretized by a virtual cubic mesh of which the elementary cube is termed geometrical cell (GC) and corresponds to a volume of 1 mm^3. The GCs belonging to the tumor are initiated

Table 1
Material parameters used in the stress/strain simulation.

Tissue	Poisson ratio ν	Young's modulus E [Pa]
Gray Matter	0.4	694
White Matter	0.4	694
Cerebrospinal Fluid	0	0